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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,475	12/05/2003	Steve Pakola	113476.122US1	3082

23483 7590 03/26/2008

WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER
KIM, TAEYOON

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
03/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/729,475	PAKOLA ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-87* is/are pending in the application.

4a) Of the above claim(s) *62 and 73-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-61,63-72 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/2008 has been entered.

Applicant's amendment and response filed on 2/14/2008 has been received and entered into the case.

Claims 1-56 are canceled, claims 85-87 are newly added, and claims 62 and 73-79 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 57-61, 63-72 and 80-87 have been considered on the merits. All arguments have been fully considered.

Response to Amendment

The declaration under 37 CFR 1.132 filed 2/14/2008 is insufficient to overcome the rejection of claims 57-61, 63-72 and 80-84 based upon Trese et al. in view of Collen et al. in further view of Wu et al. as set forth in the last Office action.

Applicant argued that plasmin and microplasmin do not share the same enzymatic activity and therefore microplasmin is not an art-accepted equivalent for plasmin based on the data shown in the declaration. The data presented in the declaration show the differences in efficiency of the enzymatic activity between plasmin and microplasmin. This argument and the declaration is not persuasive to overcome the

claim rejection under 35 U.S.C.§103, because although it appears to be the case that plasmin and microplasmin possess different efficiency in enzymatic activity, it is well known in the art that both have the same serine protease activity to hydrolyze fibrinogen, collagen, and other substrate, therefore, these two are considered to be art-accepted equivalent. Whether or not they have the identical efficiency in enzymatic activity is not the question of the equivalency for the same function. Since microplasmin retains a core catalytic domain of plasmin, with the identical sequence, a person of ordinary skill in the art recognize that these two have the same enzymatic activity, and it is known in the art that microplasmin has fibrinolytic activity according to Wu et al. and further, the declaration showed that microplasmin has such activity although it may be less efficient than plasmin for certain substrates.

The question to ask in the rejection based on art-recognized equivalency is whether microplasmin has the same activity (i.e. serine protease activity) for the same purpose (i.e. vitreolysis) as plasmin does. It is noted that the term “same activity” is not necessarily drawn to the identical efficiency in its activity. It is drawn to functional and structural characteristics shared by plasmin and microplasmin. It is clear that plasmin and microplasmin both possess fibrinolytic activity (same activity) and they have the identical domain/sequence for such activity, and because of such similarity they can be used for the same purpose of vitreolysis (lysis of collagen). Therefore, plasmin and microplasmin are considered to be art-accepted equivalent.

Even if they might not be considered as equivalents each other as argued by the applicant, although it is unlikely, a person of ordinary skill in the art would recognize

microplasmin is a suitable alternative to plasmin, and thus, it would have been obvious to a person of ordinary skill in the art to substitute plasmin with microplasmin for the intended use since microplasmin has the similar, if not the same, enzymatic activity as plasmin.

M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

Furthermore, it would have been obvious to a person of ordinary skill in the art to try microplasmin of Collen et al. for the method of Trese et al.

This is because a person of ordinary skill in the art would recognize a finite number of identified and predicted solutions for inducing vitreolysis, and also a person of ordinary skill in the art recognizes that microplasmin is known to possess the core

enzymatic activity of plasmin, as a derivative of plasmin, according to Wu et al. providing a good reason to pursue the option of utilizing microplasmin.

The Supreme Court recently states in KSR v. Teleflex (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Applicant also argued that Collen et al. do not teach the use of microplasmin in the eye, or no patent, application, reference, or catalog suggested the use of microplasmin in the eye. M.P.E.P. §2144.06 states "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Thus, the exclusive teaching or suggestion of using the equivalent (microplasmin) for another (plasmin) is not required. Although the expectation of success is not the test required to be answered, the discussion of expectation of success of combining the teaching of Collen et al. in the method of Trese et al. was provided in the previous office action and briefly, since microplasmin possesses the same catalytic domain as an enzymatic

activity as plasmin, a person of ordinary skill in the art would recognize that microplasmin would carry out the similar, if not the same, hydrolysis process as plasmin with a reasonable expectation of success.

Still further, applicant argued that there is no disclosure in prior art that microplasmin is used in eye disorder. This argument is not persuasive either. Since microplasmin is a fragment of plasmin and it possesses the similar, if not the identical, function as an enzyme, it would have been obvious to a person of ordinary skill in the art to use microplasmin in place of plasmin in vitreolysis taught by Trese et al. The combination of microplasmin of Collen et al. in the method of Trese et al. is not based on any teaching that microplasmin is known to be used in eye disorders, but based on its function equivalent to that of plasmin, and thus suitable for substitution. Again, there is no need of teaching that microplasmin is used for eye disorder since the rejection is based on equivalency of microplasmin to plasmin.

Applicant further argued unpredictability of modifying a known biological molecule such as an enzyme. However, it is known in the art that microplasmin is a derivative of plasmin comprising a core catalytic domain of plasmin and having enzymatic activity of plasmin, although it might be less efficient according to the declaration, therefore, there is no unpredictability issue for the use of microplasmin in the method of vitreolysis of Trese et al.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 57-61, 64-69, 71, 72 and 80-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trese et al. (US 5,304,118; IDS reference) in view of Collen et al. (WO 2002/50290; IDS reference) in further view of Wu et al. (US 4,774,087; IDS reference).

Trese et al. teach a method of inducing posterior vitreous detachment in a human eyes and treating certain medical disease and dysfunctions in the eye (column 1, lines 11-14) by injecting one to three units (effective amount) of human plasmin during vitrectomy (see Abstract, Figure, and columns 1 and 2). Trese et al. also teach to use the method before surgical vitrectomy or simultaneously with the removal of the vitreous (vitrectomy) (see column 2, lines 26-32).

Trese et al. do not teach the use of microplasmin made recombinantly, stabilized, or stabilized and recombinantly.

Collen et al. teach mammalian plasminogen derivatives such as human microplasmin produced recombinantly and stabilization of such recombinant proteins (see Abstract; p.9, line 24).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to replace plasmin in the method of Trese et al. with

microplasmin of Collen et al.

The skilled artisan would have been motivated to make such a modification because both plasmin and microplasmin share the same enzymatic activity as well known in the art, thus these are considered as art-recognized equivalents.

M.P.E.P. §2144.06 states "In re Scott, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963) (Claims were drawn to a hollow fiberglass shaft for archery and a process for the production thereof where the shaft differed from the prior art in the use of a paper tube as the core of the shaft as compared with the light wood or hardened foamed resin core of the prior art. The Board found the claimed invention would have been obvious, reasoning that the prior art foam core is the functional and mechanical equivalent of the claimed paper core. The court reversed, holding that components which are functionally or mechanically equivalent are not necessarily obvious in view of one another, and in this case, the use of a light wood or hardened foam resin core does not fairly suggest the use of a paper core.); Smith v. Hayashi, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.)."

Moreover, Wu et al. provide a motivation to use microplasmin over plasmin because of the advantage of the reduced size of microplasmin which does not require complexing and can act directly (see column 3, lines 34-37).

The person of ordinary skill in the art would have had a reasonable expectation of success in using microplasmin in the method of Trese et al. because the activity of microplasmin is well known to be equivalent to plasmin.

Further more, the substitution of plasmin in the method of Trese et al. with microplasmin of Collen et al. is obvious based on the suitability of microplasmin which possesses the similar, if not the same, enzymatic activity towards various substrates, as plasmin does. Therefore, microplasmin can substitute plasmin for the intended use of vitreolysis.

M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known

compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

Still further, it would have been obvious to a person of ordinary skill in the art to try microplasmin of Collen et al. for the method of Trese et al.

This is because a person of ordinary skill in the art would recognize a finite number of identified and predicted solutions for pharmacological vitreolysis, which are enzymes possessing activity for lysis of collagen since it is extremely well known in the art that vitreous membrane of eyes is composed mostly of collagen, including plasmin, microplasmin, miniplasmin, etc. and therefore a person of ordinary skill in the art recognizes that microplasmin, known to possess the core enzymatic activity of plasmin, as a derivative of plasmin, according to Wu et al. is one of the finite number of enzymes for pharmacological vitreolysis and thus there is a good reason to pursue the option of utilizing microplasmin.

The Supreme Court recently states in KSR v. Teleflex (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that

instance the fact that a combination was obvious to try might show that it was obvious under §103."

Although Trese et al. in view of Collen et al. in further view of Wu et al. do not particularly disclose the range of effective amount of microplasmin being 0.005 mg to 0.2 mg per eye. It would have been obvious for a person of ordinary skill in the art at the time of invention made to optimize the amount of microplasmin for the intended use of vitreolysis. The selection of effective amount of microplasmin would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that identification of the amount of microplasmin sufficient to induce posterior vitreous detachment or vitreolysis is critical to effectively treat the patients. A holding of obviousness over the cited claims is therefore clearly required. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages. See *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382.; See also M.P.E.P. § 2144.05.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 57, 63, 66 and 70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Trese et al. et al. (supra) in view of Collen et al. (supra) in further view of Wu et al. (supra) and Tanaka et al. (2000; IDS reference AX filed on Jan. 14, 2005).

Claims are drawn to a method of liquefying a vitreous and/or inducing posterior

vitreous detachment of an eye of a subject, comprising contacting the vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 57); a limitation to the method being performed in the absence of vitrectomy (claims 63 and 70); a method of treating a vitreoretinal disease or disorder of an eye of a subject, comprising contacting a vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 66).

Trese et al. in view of Collen et al. in further view of Wu et al. renders claims 57 and 66 obvious (see above).

Trese et al. in view of Collen et al. in further view of Wu et al. do not teach that the method of claims 57 and 66 being performed in the absence of subsequent vitrectomy.

Tanaka et al. teach that pharmacological vitrectomy referring to the use of enzymes (e.g. microplasmin) in an effort to liquefy vitreous during or before performing vitreous surgery (vitrectomy). Tanaka et al. further teach the use of plasmin to make the vitreous surgery easier for better outcome or to avoid vitrectomy (see abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the method of Trese et al. in view of Collen et al. in further view of Wu et al. without additional/subsequent vitrectomy. The skilled artisan would have been motivated to make such a modification because Tanaka et al. teach that the use of pharmacological vitrectomy may allow avoiding subsequent vitrectomy.

The person of ordinary skill in the art would have had a reasonable expectation

of success in using the method of Trese et al. in view of Collen et al. in further view of Wu et al. without further vitrectomy because effective amount of microplasmin would sufficiently achieve posterior vitreous detachment.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford Jr/
Primary Examiner, Art Unit 1651

Taeyoon Kim
AU-1651